IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl. No. : **10/621,760**

Applicants : **David L. Lewis *et al.***

Filed : **07/17/2003**

Art Unit : **1633**

Examiner : **Popa, Ileana**

Docket No. : **Mirus.030.09.2**

For: **Compositions and Processes Using siRNA, Amphipathic Compounds and Polycations**

Commissioner of Patents
PO Box 1450
Alexandria, VA 22313-1450

APPELLANT'S BRIEF under 37 CFR 1.192

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1. Real party in interest:

The real parties in interest are: David L. Lewis, James E. Hagstrom, Hans Herweijer, Aaron G. Loomis, Sean D. Monahan, Jon A. Wolff, Vladimir Trubetskoy and, by assignment, Mirus Corporation, which changed its name to Mirus Bio Corporation under the laws of the State of Delaware, which again changed its name to Mirus Bio LLC under the laws of the State of Wisconsin and is located at 545 Science Drive, Madison, WI 53711.

2. Related appeals and interferences:

There are no interferences known to appellant, the appellant's legal representative, or assignee which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

3. Status of Claims:

Claims 1-3, 5 and 9 have been rejected and are hereby appealed.

Claims 4 and 6-8 have been canceled; claims 10-20 have been withdrawn.

4. Status of amendments:

No Amendments have been filed subsequent to the final rejection.

5. Summary of claimed subject matter:

The first independent claim, claim 1, is a composition for transfecting a siRNA into animal cells using a ternary complex comprising siRNA, an amphipathic compound, and a polycation. The initial support for the claim is found in the specification on page 4, lines 28-33.

The second and last independent claim, claim 5, is a process for transfecting an animal cell in vitro with a siRNA comprising: adding to the cell in a solution a composition comprising an amphipathic compound, an effective amount of a polyvinylamine, and a siRNA, wherein the composition facilitates entry of the siRNA into the cell. This claim has initial support in the specification on page 6, lines 17-22.

The delivery of siRNA is very difficult and there is not another compound that was comparable at the time the claims were filed. The compound and process are unique delivery technologies for transfecting siRNA to animal cells in a manner that is not toxic and where the siRNA can function.

6. Grounds of rejection to be reviewed on appeal:

Whether claims 1-3, 5 and 9 are unpatentable on the ground of non-statutory obviousness type double patenting as being unpatentable over claims 1, 2, 6, and 7 of Wolff *et al.* (U.S. Patent 5,744,335) in view of Boussif et al. (WO 01/59087) and Fire et al. (U.S. Patent No. 6,506,559).

Whether claims 1-3, 5 and 9 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Boussif et al. (WO 01/5907) in view of Wolff *et al.* (U.S. Patent No. 5,744,335), Bischoff *et al.* (U.S. Patent No. 6,291,423) and Fire *et al.* (U.S. Patent No. 6,505,559).

7. Argument:

7.1. Double Patenting: nonstatutory obviousness type double patenting as being unpatentable over claims 1, 2, 6, and 7 of Wolff *et al.* U.S. Patent No. 5,744,335, in view of both Boussif *et al.* (WO 01/59087) and Fire *et al.* (U.S. Patent No. 6,506,559).

7.1.1. Claims 1-3, 5, and 9: The final Action states that although the conflicting claims are not identical, they are not patentably distinct from each other because they are obvious variants. On page 3, the Action states that the claims of Wolf recite a process for transfecting a polynucleotide into a mammalian cell by delivering a composition comprising an amphipathic compound, a histone, and the polynucleotide, wherein encapsulation of the polynucleotide by the amphipathic compound is not required for transfection (claims 1 and 2), wherein the amphipathic compound is a 1,4 disubstituted piperazine and wherein the substituting groups are C6 to C24 alkenes (claims 6 and 7). The specification defines that R1 andR2 could be the same and the polynucleotide can be an antisense oligonucleotide(Summary of the invention, lines 54-67, column 7, lines 14-17). The patent claims do not recite polyvinylamine (PVA).

The lack of reciting polyvinylamine is a key. To this point, Applicants previously submitted a 1.132 Declaration with experimental evidence that histone, an amphipathic compound, forms an effective plasmid DNA delivery agent, while polyvinylamine does not form an effective plasmid DNA delivery agent.

To negate this argument, the examiner presents that Boussif et al. teach a method for introduction of antisense oligonucleotide into cells by using a composition comprising polyvinylamine, and amphipathic compound, and an antisense oligonucleotide thereafter citing a laundry list from the Boussif et al. application. Applicant has argued that Boussif et al. has put

forward a laundry list of compounds without providing evidence or a logical presentation that they actually work.

It is well known, as stated by the Federal Circuit, that simply mentioning compounds in a patent does not suffice as a specification description to give the patentee outright claim to all the structures. The disclosure must reasonably guide one skilled in the art to select the specific subsets of moieties recited in the patent's claims. (Fujikawa v. Wattanasin, 93 F.3d 1559, 1571, 39 USPQ2d 1895, 1905 (Fed. Cir. 1996)). The written description must contain some statement that will direct a skilled artisan to select the compound. Pressure Products Medical Supplies, Inc. v. Greatbatch Ltd., No. 2008-1602 (Fed. Cir. Mar. 31, 2010).

Furthermore, Boussif does not recite siRNA but recites "antisense" – a completely different compound in the context of delivery. The examiner explains this away by combining yet another citation that recites siRNA and concludes that the combination of the three prior art references would be obvious.

Applicants assert that there is no motivation to combine the three references and that even if one were to accept the unlikely combination of references cited by the examiner, the 1.132 Declaration cuts directly to the question of obviousness type double patenting. Applicants have presented evidence, which was derived as described in the cited Wolff et al. reference, that teaches away from the combination of the three compounds. The Declaration indicates that the combination of the three recited compounds would not work i.e. the combination of references contain compounds that when combined in the correct formulation (not provided) may allow delivery of plasmid DNA or antisense DNA, however, could not provide a method to transfect siRNA. Therefore, it would not be obvious to use the polyvinylamine with an amphipathic compound and siRNA to improperly extend the claims of the Wolff et al. patent.

7.2. Rejection under 35 U.S.C. 1 03(a) as being unpatentable over Boussif et al. (WO 01 /59087), in view of each Wolff et al. (US Patent 5,744,335), Bischoff et al. (U.S. Patent No. 6,291 ,423), and Fire et al. (U.S. Patent No. 6,506,559).

7.2.1. Claims 1-3, 5, and 9: As with the previous obvious type double patenting issue the examiner uses the laundry list provided in the Boussif et al. application. The Action states that Boussif et al., Wolf et al., and Bischoff et al. teach antisense oligonucleotides and not siRNA (claims 1 and 5), however, Fire et al. teach that siRNAs are more efficient than antisense oligonucleotides in inhibiting the expression of target genes.

To a person having knowledge in the art, the delivery of antisense molecules is not similar to the delivery of siRNA. An antisense molecule as described at the time of the cited prior art consisted of DNA containing hundreds of bases in contrast to siRNA which is around 20 base pairs. In the art of delivery, that difference in nucleic acid size translates into different problems for delivery. Combinations of compounds that assist in delivery for one size and/or type of nucleic acid may not assist the delivery of another size/type of nucleic acid. In the present case, the combination of molecules listed in the cited prior art would not deliver siRNA as shown in the 132 Declaration.

A rejection under 35 U .S.C. 103(a) would be appropriate if a person of ordinary skill would have been motivated to modify a primary reference by deleting features thereof or by interchanging with or adding features from pertinent secondary references. However, if the proposed combination of the references so alters the primary reference that its broad function can no longer be carried out, the combination of the prior art would not have been obvious to a designer having ordinary skill in the art.

In this case, the examiner's combination of references alters the primary reference by cherry picking terms out of the Boussif et al. specification. The Action points out that Boussif et al. indicates that one can combine

an amphipathic compound with polyvinylamine and antisense for efficient delivery. The examiner is assuming that the antisense molecules described in Boussif et al. are similar to siRNA when in fact they are more similar to plasmid DNA for purposes of delivery. In fact, Boussif et al. provides one single working example. That example describes the use of cationic lipids (not polyvinylamine) and plasmid DNA (not antisense) and there is no mention of an amphipathic compound. The examiner's incorrect assumption that the simple listing of the term antisense in Boussif et el. makes it similar to siRNA significantly alters the primary reference such that its broad function is not applicable.

It is clear to those familiar with biochemical patents and patent applications that the background and summary portions are many times filled with compounds that may or may not be related (in this case: in relation to delivering siRNA) to the compounds provided, described and used in the examples.

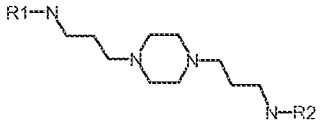
Applicants again invoke the reminder from the Federal Circuit that a "laundry list" disclosure of every possible moiety does not constitute a written description of every species in a genus because it would not "reasonably lead" those skilled in the art to any particular species. (Fujikawa v. Wattanasin, 93 F.3d 1559, 1571, 39 USPQ2d 1895, 1905 (Fed. Cir. 1996)). The Boussif et al. reference talks about antisense but provides one working example, not about the delivery of antisense molecules, but of the delivery of plasmid DNA. Wolff et al. describes delivery of plasmid DNA. Fire et al. describes siRNA. The 1.132 Declaration shows that plasmid DNA is not effectively delivered using an amphipathic compound with polyvinylamine. Applicants' show and claim efficient delivery of siRNA using an amphipathic compound and polyvinylamine.

A reasonable person having knowledge in the art who reviewed the cited prior art would not have an expectation that substituting any size/form of nucleic acid for plasmid DNA as shown in Wolff et al. would provide

efficient delivery of that species of nucleic acid. Therefore, a combination of compounds picked from an extensive untested list in the cited prior art would not be obvious.

8. Appendix, Copy of the Claims:

1. (previously presented) A composition for transfecting an siRNA into a cell in vitro comprising: an amphipathic compound, a polyvinylamine, and said siRNA.
2. (previously presented) The composition of claim 1 wherein the amphipathic compound has the structure comprising:



wherein R1 and R2 consist of C6-C24 alkenes.

3. (original) The composition of claim 2 wherein R1 and R2 of the amphipathic compound are the same.
4. (canceled)
5. (previously presented) A process for transfecting an animal cell with a siRNA comprising: adding to the cell in a solution a composition comprising an amphipathic compound, an effective amount of a polyvinylamine, and a siRNA, wherein the composition facilitates entry of the siRNA into the cell.
6. (previously presented) The process of claim 5 wherein the animal cell is in vivo.
7. (previously presented) A process of claim 5 wherein the animal cell is in vitro.
8. (previously presented) The process of claim 5 wherein the animal cell is ex vivo.
9. (previously presented) The process of claim 5 wherein the animal cell is a mammalian cell.

9. Appendix, Evidence:

The evidence consists of a §1.132 Declaration entered into the record in an Amendment and Response filed on December 5, 2007.

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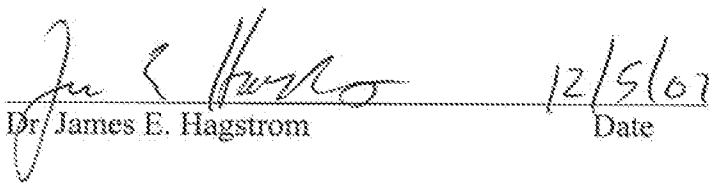
DECLARATION UNDER 37 C.F.R. ' 1.132

Dear Commissioner

I, James E. Hagstrom, hereby declare as follows:

1. I am an inventor of the above captioned application.
2. I have submitted, with the amendment filed 12-5-2007, a Declaration containing experimental material illustrating: delivery of siRNA to mammalian cells using a complex consisting of an amphipathic compound, DNA and either histone or ethoxylated polyethyleneimine.
3. The complexes were prepared as taught in Wolff et al. (U.S. Patent 5,744,335).
4. The amphipathic compound of the Declaration experiments was identical to that used by Wolff et al. (U.S. Patent 5,744,335).

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.



Dr. James E. Hagstrom 12/5/07
Date

Cos7 cells, 293 cells, or 3T3 cells were initially transfected with a plasmid DNAs encoding the Firefly luciferase gene and the Renilla luciferase genes, resulting in cells that expressed these two luciferase proteins. These cells were then transfected with 5 nM Firefly luciferase siRNA using either ethoxylate polyethyleneimine (ePEI) + amphipathic compound or histone + amphipathic compound.

Successful delivery of the Firefly luciferase siRNA to cells expressing the Firefly luciferase gene results in knockdown (inhibition) of Firefly luciferase gene expression. Thus, delivery of Firefly luciferase siRNA directly correlates with knockdown of Firefly luciferase gene expression. Higher knockdown means more efficient delivery, while lower knockdown means less efficient or no delivery. As shown in the table below, siRNA was efficiently delivered with ePEI + amphipathic compound: 71% to 90% knockdown. In contrast, histone + amphipathic compound was not an effective siRNA delivery reagent: 0% knockdown.

The histone + amphipathic compound was the same composition as that used in U.S. Patent 5,744,335. The ePEI + amphipathic compound was the same as that described in Application 10/621,760. The amphipathic compound used with histone was the same as that used with ePEI.

transfection reagent	Luciferase expression	% knockdown
none	1.0000	0.0000
ePEI + amphipathic compound	0.0960	0.9040
histone + amphipathic compound (ratio 1)	*1.0760*	*−0.0760*
histone + amphipathic compound (ratio 2)	*1.1820*	*−0.1820*
histone + amphipathic compound (ratio 3)	*1.1980*	*−0.1980*
ePEI + amphipathic compound	0.2830	0.7170
histone + amphipathic compound	*1.0398*	*−0.0398*
ePEI + amphipathic compound	0.2222	0.7778
histone + amphipathic compound	*1.0344*	*−0.0344*

10. Appendix, Related proceedings:

none

These pages 1-19 are
respectfully submitted,

/Mark K Johnson/
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I hereby certify that this correspondence is being transmitted to the USPTO addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on this date: February 17, 2011.

/Mark K Johnson/
Mark K Johnson